Medical Importance Of Parasites.

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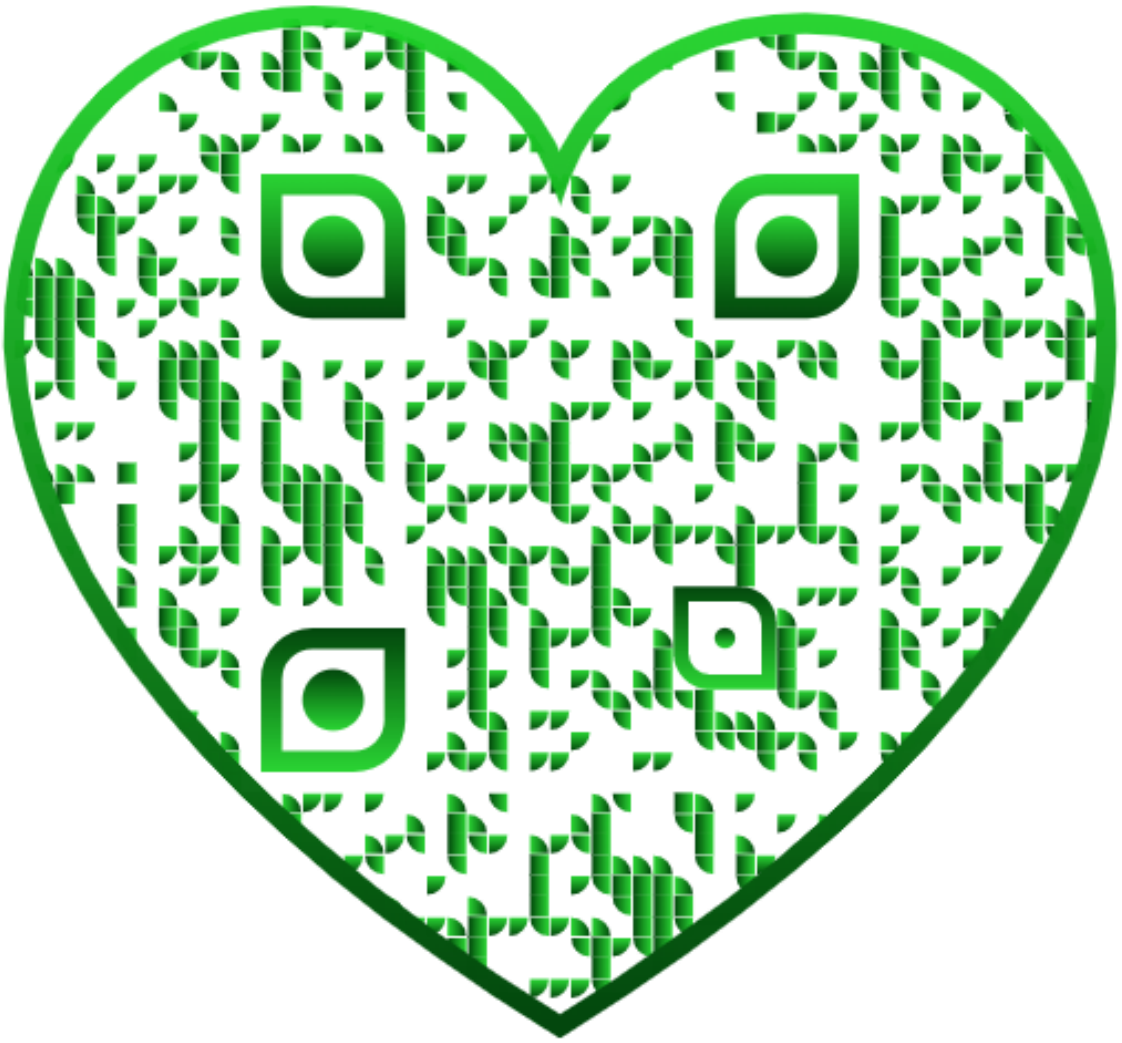


Introduction: the goodness of parasites?

- The goodness of parasitism' was initially coined by David Lincicome while he was Professor of Zoology at Howard University, he performed numerous experiments using a variety of protozoan and nematode parasites of rats and mice.

- He observed that the parasitized animals often performed better in terms of body weight gain, longevity, and certain physiological parameters than those that were parasite-free.

- ways of using parasites to our advantage:

1- many parasites have evolved molecules that help them exploit their host and these may prove useful as sources of novel pharmaceutically-active substances.

2- parasitism may be helpful for maintaining a healthy immune system.

3- The effects of parasites on their hosts can also be used for the treatment of specific medical conditions and to control pest animals and plants.

4- Parasites have even been implicated in criminal investigations and some workers have seen fit to coin the term 'forensic parasitology'.

Parasites as sources of novel pharmaceutically active compounds.

Parasites as sources of novel pharmaceutically-active compounds.

- Parasites produce a variety of secretions and excretions and some of these include compounds with potentially useful pharmacological properties.
- Between the 1930s and 1950s there was considerable interest in both Russia and America in the potential of extracts derived from Trypanosoma cruzi to treat certain forms of cancer.
- The results of these studies were ambiguous, with some workers claiming remarkable effects and others finding none at all or even harmful toxicity.
- Although products based on Trypanosoma cruzi extracts were eventually marketed, the active ingredients were never identified and interest in this line of research ultimately ceased.

Parasites as sources of novel pharmaceutically-active compounds.

- There has been much more success in developing pharmacologically useful products from blood-feeding parasites.
- Most blood-feeding (haematophagous) organisms produce chemicals that inhibit platelet aggregation and one or more of the serine protease enzymes (coagulation factors) involved in the tissue factor pathway.
- For example, the leech Hirudo medicinal is produces a protein called 'calin' that interferes with platelet aggregation and a polypeptide called hirudin that interferes with fibrin formation. Calin prevents the formation of a platelet plug by interfering with the interaction between platelets and collagen.
- Another compound, 'hirudin' is produced in a variety of isoforms and complexes with α-thrombin (coagulation factor IIa) and there by prevents it from catalyzing the conversion of fibrinogen to fibrin.

Parasites as sources of novel pharmaceutically-active compounds.

- Hirudin is currently employed to treat conditions as varied as topical bruising and heart disease.

- It has the advantages.

1. Low Toxicity.
2. Does Not Interfere With Any Coagulation Factors apart from - thrombin or any other physiological processes
3. It Does Not Appear To Stimulate An Immune Response.
4. Eliminated Completely Via The Kidneys.

Medicines Extracted And Manufactured from leech protein ‘hirudin’.

NDC 65293-001-01
Angiomax
(bivalirudin)
FOR INJECTION
250 mg Rx Only
For Intravenous Use Only.
For Single-Dose Only.
Discard Unused Portion.
Product of Belgium
Each vial contains 250 mg bivalirudin equivalent to an average of 275 mg bivalirudin trifluoroacetate with 125 mg Mannitol and Sodium Hydroxide for pH adjustment. Add 5 mL of Sterile Water for Injection. Each mL contains 50 mg of bivalirudin.
Marketed by:
THE MEDICINES COMPANY
Parsippany, NJ 07054
Store at 20-25°C (68-77°F)
Excursions to 15-30°C permitted
[See USP Controlled Room Temp.]
NDC 65293-001-01
Angiomax
(bivalirudin)
FOR INJECTION
250 mg
For Intravenous Use Only
Rx Only

Trade Name: Angiomax®

Generic name:- Bivalirudin

Date Of FDA Approval: 12/15/2000.

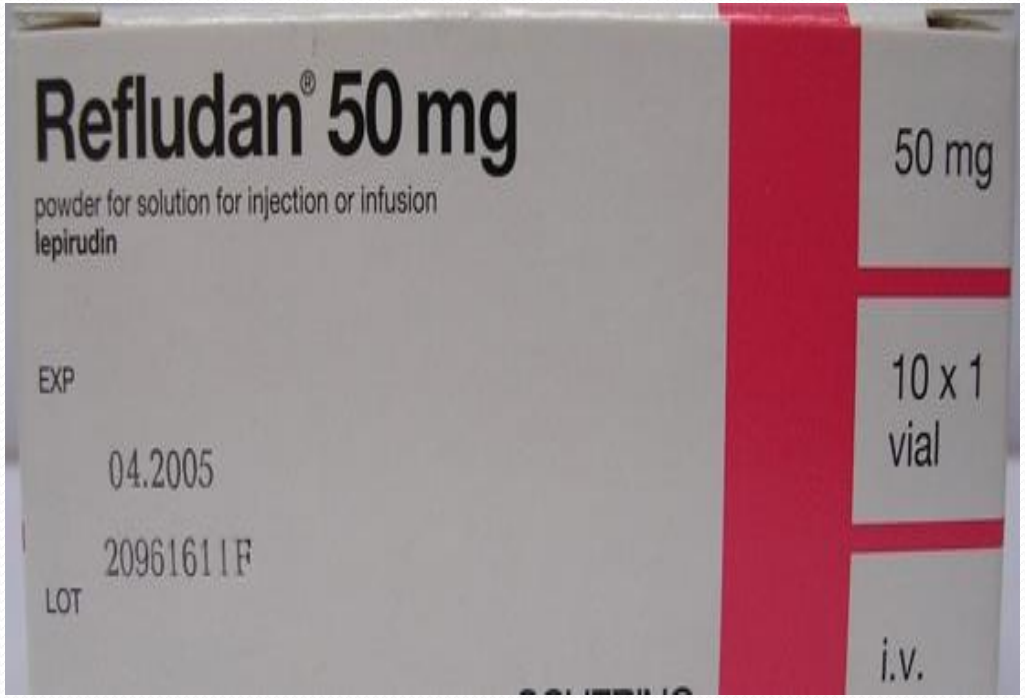
Company: The MEDICINES Company.

Mechanism Of Action: Direct Thrombin Inhibitor & Inhibit Platelets Activation.

Uses : Its Has Been FDA-approved For Treatment Of Percutaneous Coronary Intervention (PCI).

Category: Anticoagulant..

Medicines Extracted And Manufactured from leech protein ‘hirudin’.



Trade Name: Refludan®
Generic name:- Lepirudin
Date Of FDA Approval: 3/6/1998.
Company: Hoechst Marion Roussel.
Mechanism Of Action: Direct Thrombin Inhibitor & Inhibit Platelets Activation.
Uses : Its Has Been FDA-approved For Treatment Patients With thrombosis Related to heparin induced thrombocytopena.
Category: Anticoagulant..

Medicines Extracted And Manufactured from leech protein ‘hirudin’.

Trade Name: Iprivask®

Generic name:- Desirudin For Injection

Date Of FDA Approval: 4/4/2003.

Company: Aventis pharmaceutical, Inc.

Mechanism Of Action: Direct Thrombin Inhibitor & Inhibit Platelets Activation.

Uses : Its Has Been FDA-approved For for the prevention of deep vein thrombosis (DVT), which may lead to pulmonary embolism

Category: Anticoagulant..

Parasites as sources of novel pharmaceutically-active compounds.

- The hookworm Ancylostoma caninum produces a protein called HPI-1 that prevents platelets from aggregating together via fibrinogen and also a range of specific inhibitors of coagulation factors VIIa and Xa.
- Nematode anticoagulant peptides derived from Ancylostoma caninum have been used successfully to prevent thrombus formation following surgery but further clinical trials are needed to determine fully their effectiveness and safety
- found that macaque monkeys injected with a potentially lethal dose of Ebola virus did not develop the disease or expressed only mild symptoms if they were subsequently treated with recombinant nematode anticoagulant protein c2 (rNAPc2).
- NAPc2 is one of the anticoagulant proteins produced by Ancylostoma caninum and exerts its effect by inhibiting the factor VIIa/tissue complex through a unique mechanism.
- NAPc2 initially interacts with coagulation factor Xa and the resultant binary complex then inhibits factor VIIa of the factor VIIa/tissue factor complex.
- rNAPc2 inhibits angiogenesis and both primary and secondary metastatic tumour growth in mice.
- Interestingly, another recombinant nematode anticoagulant protein derived from Ancylostoma caninum, rNAP5, that specifically inhibits coagulation factor Xa has no effect on tumour growth.

The importance of parasites for the maintenance of a healthy immune system.

The importance of parasites for the maintenance of a healthy immune system

- Parasitic helminths stimulate a Th2 type cell-mediated immune response in which the cytokines interleukin-4, interleukin-5, interleukin-10, and interleukin-13 are produced.

- The TH1 response is principally stimulated by and directed against intracellular parasites and involves the production of gamma interferon.
- If the Th1 response is not controlled, it can result in damage to healthy tissues and can also lead to the development and maintenance of autoimmunity.

- Helminths interact with their host's immune system in a wide variety of ways. For example, direct physical damage caused by their feeding and movement will induce an immune reaction & many helminth secretions and excretions are immunogenic.

The importance of parasites for the maintenance of a healthy immune system

- The parasites may directly or indirectly influence the gut microbial flora through their feeding and secretions or excretions, which this may in turn influence the host's digestion and immunity.

- substances with antimicrobial activity have been detected in the excretory/secretory products of **Trichuris suis.**

- Helminth infections cause eosinophilia in which the proportion of eosinophils in the general circulation can increase from 2–5% of the white blood cells to as high as 40%.

- However, despite this, helminth infections appear to protect against the development of allergies.

- An alternative explanation for the negative association between helminth infection and predisposition to allergies could be that those who are atopic are more resistant to helminths than the general population.

The useful parasite in type 1 diabetes mellitus .

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- Type 1 diabetes mellitus is caused by the autoimmune destruction of the insulin-producing beta cells in the Islets of Langerhans in the pancreas.

- Experiments with non-obese diabetic (NOD) mice have indicated that various helminths or their products can protect the mice from developing spontaneous type 1 diabetes.

- The reason for this protective effect may be related to the fact that helminths tend to cause a predominantly Th2 response and the Th1 response is reduced.

- Some helminth infections induce interleukin-10 and it is possible that this may contribute to preventing the development of autoimmune conditions including type 1 diabetes mellitus.
  For example, children infected with Schistosoma haematobium produce elevated levels of interleukin-10 and this has been suggested as a reason why they are less likely to develop atopy.

The useful parasite in type 1 diabetes mellitus .

- The filarial nematode Litomosoides sigmodontis induces regulatory T cell activity and this is thought to contribute to the parasite preventing the development of type 1 diabetes mellitus and allergen sensitivity in mouse model systems.

- The Schistosoma mansoni antigens protect the non-obese diabetic mice from developing diabetes and this may, at least in part, be a consequence of the increased natural killer T cell activity.

- Helminth infections bring about elevated levels of alternatively activated macrophages and these then suppress the Th1 response and could thereby help protect against the development of type 1 diabetes

The useful parasite in Irritable bowel syndrome (IBS).

The useful parasite Irritable bowel syndrome (IBS).

- Irritable bowel syndrome (IBS) is a chronic condition involving altered bowel habits in which the patient experiences abdominal pain, constipation, and diarrhoea.
- Some doctors consider IBS to be a psychosomatic disorder but there is strong evidence that it is linked to alterations in the gut bacterial flora and inflammatory changes.
- In some cases of IBS, the changes can be linked to taking antibiotics or to gastrointestinal infections.
- In the latter situation, the condition is known as post-infectious IBS.
- The role of helminth parasites in the development of IBS is uncertain. As a rule, the prevalence of IBS tends to be low in countries in which gut helminth infections are common.
- The protozoan Blastocystis hominis has been linked to post-infectious IBS but much of the evidence to date has been contradictory.
- This has led to suggestions that gut helminth infections might protect against the development of IBS – provided the numbers of worms remain low.
- This protection might result from the helminths inducing a predominantly Th2 type immune response within the intestinal mucosa which prevents the development of a chronic inflammatory response.

The useful parasite Inflammatory bowel disease

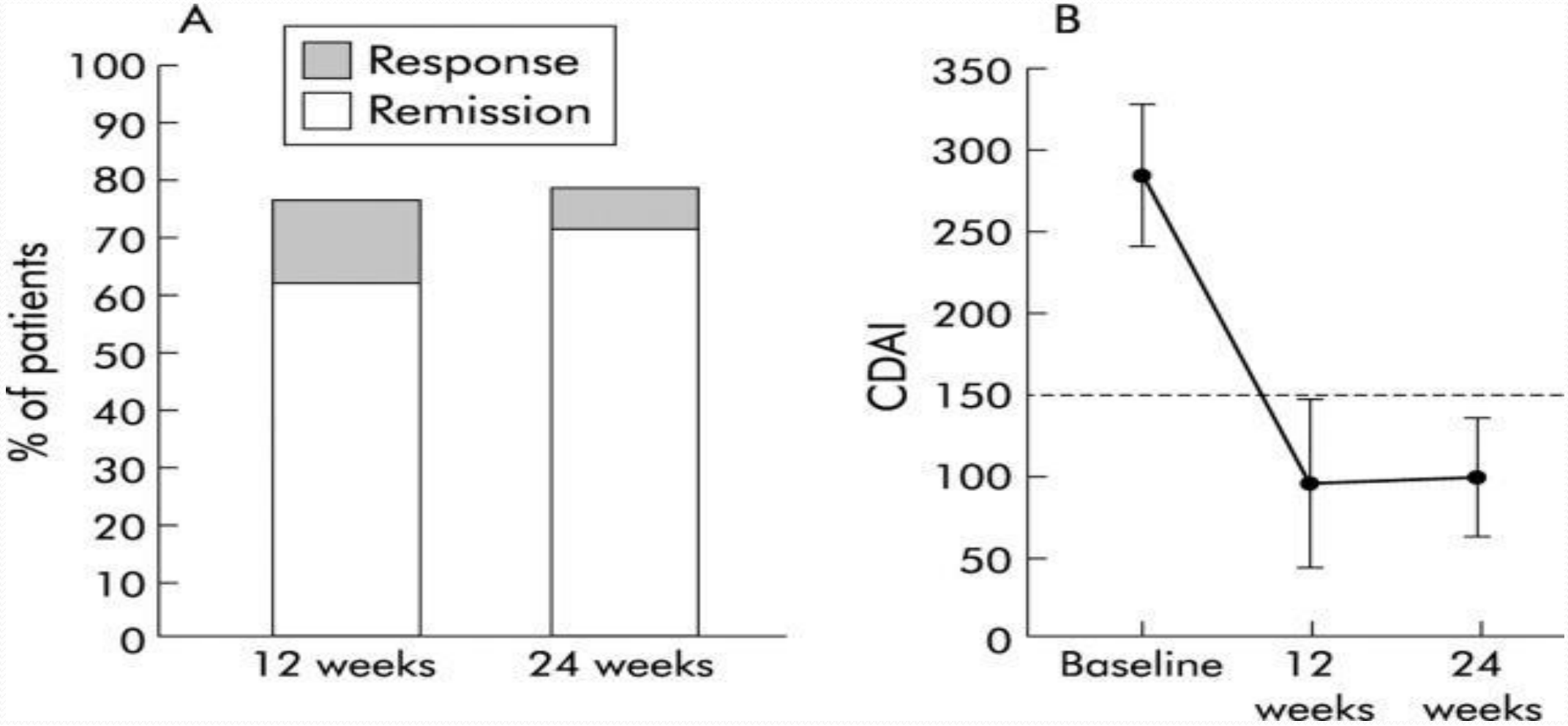
- Inflammatory bowel disease is a generic term for a group of chronic inflammatory diseases of which Crohn's disease and ulcerative colitis are the principal forms.
- Both Crohn's disease and ulcerative colitis are becoming increasingly common in developed countries but they are relatively rare in developing nations.

- In rodent models of inflammatory bowel disease, rats or mice given an intra-rectal injection of trinitrobenzene sulphonic acid (TNBS) develop an inflammation in their colon (colitis) that results from a Th1 inflammatory response.
- However, if the rodents are infected with the nematodes Trichinella spiralis or Schistosoma mansoni, then they are protected from developing TNBS-induced colitis.

- This appears to be due to the interleukins produced as a consequence of the Th2 response against the helminths causing a down-regulation of the Th1 response.

The useful parasite Inflammatory bowel disease

- Trichuris suis therapy in Crohn's disease .
- Link of study: https://plumbed.ncbi.nlm.nih.gov/15591509/



The use of parasites to treat medical conditions.

The use of parasites to treat medical conditions

1- Helminth therapy.

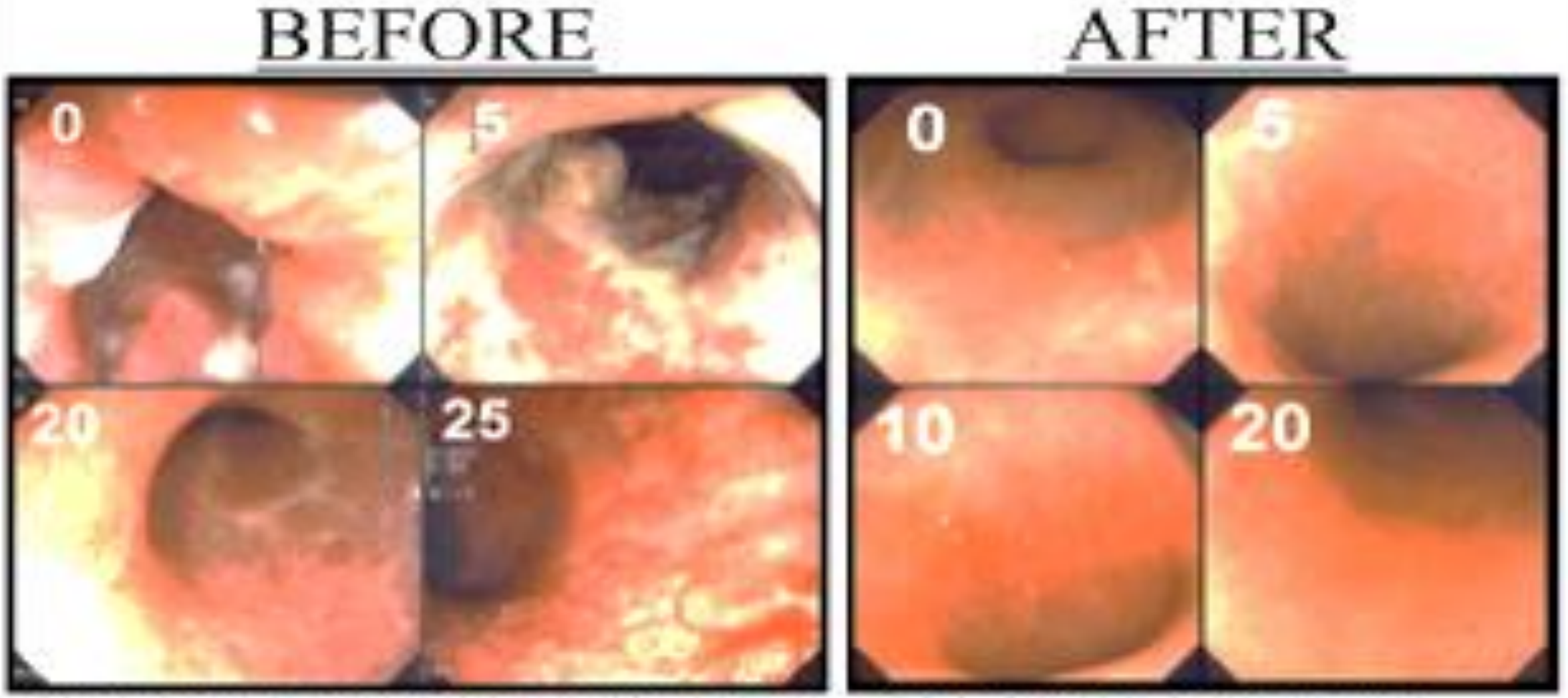
- Epidemiological data and experimental studies using rodent models indicate that parasitic helminth infections may protect against the development of certain autoimmune conditions.

- helminth parasites have complex immunological relationships with their hosts and therefore it is unlikely that any protective effect will be conferred by just one or a few helminth-derived substances.

- Parasite infections can be considered to be living drug pumps that deliver a regular dose of chemicals which is more convenient for the patient than taking pills or receiving injections.

The use of parasites to treat medical conditions

- To date, most work on helminth therapy has been done using the whipworm Trichuris suis and to a lesser extent the hookworm Necator americanus.
- Both of these nematodes are capable of causing serious pathology, but low worm burdens in otherwise healthy, well-nourished individuals are considered to cause little harm.
- Trichuris suis is a common parasite of pigs and found throughout the world has been tried as treatment for inflammatory bowel disease, with some promising results and a preliminary study indicates that it may also be useful for treating multiple sclerosis.
- Although Trichuris suis infects humans, there are contradictory reports about whether the worms are capable of reaching sexual maturity within humans and then producing viable eggs.
- Necator americanus has been trialled for the treatment of inflammatory bowel disease and asthma



Endoscopic evaluation of a patient with ulcerative colitis before and after therapy with *Trichuris suis*. Treatment with *T. suis* afforded healing of the inflammation as seen by flexible sigmoidoscopy. Numbers in upper left corner indicate location (centimeters from anal orifice) where photograph was made.

2- using fly larvae (maggots) to encourage wound healing

Maggot Therapy (Larval Therapy)

Maggot therapy is a widely accepted treatment for chronic, non-healing wounds. Used larvae feed mainly on pus & necrotic tissue.

The maggots are painless, effective and offer a safe way to perform debridement (removal of dead tissues) Removal of larvae is easy. Rarely invade healthy tissue.

2- using fly larvae (maggots) to encourage wound healing

Box 8.2 Larval therapy in practice

A hole is cut in a hydrocolloid dressing the size and shape of the wound and this is applied to the wound site. This confines the larvae to the wound site and protects the surrounding healthy skin; 5–10 sterile first instar larvae (~2mm in length) per cm^2 of wound are placed on a sheet of semipermeable nylon mesh (e.g., LarvE™ NET, Tegaporc™: 3M) and this is then laid on the surface of the wound. The hydrocolloid dressing is then covered with waterproof adhesive tape so as to confine the larvae to the wound site. After 3 days the dressings and the larvae, which have usually grown to approximately 9 mm by this time, are gently washed out of the wound. The procedure is then repeated until the wound is clean and all the necrotic tissue is removed. Alternatively, the maggots may be applied to the wound site in a Biobag (BioMonde, Germany) which contains a set number of larvae (e.g. 50 or 100) confined between two layers of a polyvinyl alcohol hydro sponge (Preus *et al.*, 2004). Whichever approach is adopted, most wounds only require one to three treatments. Most patients are positive about the benefits of this treatment although a few find it psychologically repugnant. During treatment, most patients experience either a decrease or at least no increase in their level of pain beyond a 'tickling sensation' although some do find the treatment painful (Gupta, 2008; Wolff and Hansson, 2003).

The use of parasites to treat medical conditions

3- Malaria therapy (malariotherapy)

- Malaria therapy was initially developed to treat the disease syphilis.
- Syphilis is a serious disease but it is currently treatable with antibiotics and is sometimes considered to be just one sexually transmitted disease among many.
- syphilis is caused by the spirochaete bacterium Treponema pallidum and is usually transmitted through sexual intercourse, although it can also cross the placenta in pregnant women and cause congenital syphilis.

The use of parasites to treat medical conditions

- Plasmodium ovale came to be the most frequently used species of Plasmodium for malaria therapy because it induces a high fever but seldom causes serious pathology.
- Initially, transmission was undertaken by withdrawing 2–5 ml blood from the vein of an infected donor and injecting this subcutaneously into the recipient.
- The results were rather variable and were affected by the level of fever induced and the severity of the patient's syphilitic symptoms.
- The physiological and immunological basis of how malaria therapy worked is still not known.

Box 8.4 The development of malaria therapy (malariotherapy)

Julius Wagner Ritter von Jauregg (1857–1940) (usually referred to as Wagner-Jauregg) was awarded the Nobel Prize for Medicine in 1927 for his work in developing malaria therapy for the treatment of neurosyphilis. Wagner-Jauregg worked as a psychiatrist at a clinic in Vienna and noted how the mental health of some of his patients improved following illnesses that induced high fever. He decided to carry out a more in-depth series of observations and recorded that patients with neurosyphilis showed considerable improvement in their condition following bouts of fever associated with erysipelas and tuberculosis. He tried various means of inducing fever in his patients but these had little effect on their mental well-being. He ascribed this to the fevers not raising the body temperature high enough. He thought that malaria would be the ideal means by which this could be achieved but lacked a source of the infection. Eventually, in 1917, a soldier was admitted to his ward suffering from shell-shock who had caught benign tertian malaria (*Plasmodium vivax*) while serving in the Crimea. He took blood from the soldier and injected it into nine patients suffering from neurosyphilis. After they had experienced at least seven episodes of fever he treated them with quinine. Six of the patients subsequently improved so much that they were able to leave the clinic and return to work. They were not actually cured of syphilis and four of them suffered relapses in later years but it should be remembered that their prognosis at the time of their treatment was exceedingly bleak. Wagner-Jauregg was encouraged to continue with his studies and publish his findings which were met with considerable enthusiasm. Malaria therapy (sometimes referred to as 'malariotherapy') was quickly adopted in Europe and around the world and became the principal means of treating neurosyphilis. Indeed, malaria therapy continued to be used in specific cases in the USA until the 1960s and in the UK in the 1970s.

Thank you